THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Phase II study of Minocycline vs. Placebo to Prevent Treatment Induced Neuropathy in Multiple Myeloma
2006-0022

Core Protocol Information

Short Title	Prevention of Treatment Induced Neuropathy in Multiple Myeloma
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Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objectives

1. To compare the safety of minocycline vs. placebo in patients receiving induction therapy for multiple myeloma with a regimen containing thalidomide, and/or bortezomib

2. To compare the effect of minocycline vs. placebo on peripheral nerve function, as determined by a change in touch detection threshold, among patients receiving induction therapy of previously untreated multiple myeloma with a regimen containing thalidomide, and/or bortezomib.

1.2 Secondary Objectives

1. To evaluate the effect of minocycline vs. placebo on patients' neuropathic symptoms during induction therapy of previously untreated multiple myeloma with a regimen containing thalidomide and/or bortezomib.

2. To evaluate the effect of minocycline vs. placebo on serum cytokine levels in patients receiving induction therapy of previously untreated multiple myeloma with a regimen containing thalidomide and/or bortezomib.

3. To evaluate the effect of minocycline vs. placebo on neurocognitive function in patients receiving induction therapy of previously untreated multiple myeloma with a regimen containing thalidomide and/or bortezomib.

4. To evaluate the effect of minocycline vs. placebo on daytime somnolence in patients receiving induction therapy of previously untreated multiple myeloma with a regimen containing thalidomide and/or bortezomib.

2.0 Background

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 14% of hematologic malignancies. More than 15,000 cases of this disorder are diagnosed in the United States each year. Multiple myeloma is twice as common in African Americans as in white persons, and is slightly more common in men than in women (1). The median age at onset is 66 years, and only 2% of patients are younger than 40 years at diagnosis. (2) Until the last 5 years, combination therapy with melphalan and prednisone (MP) has been the mainstay of therapy. However, the demonstrated benefits of autologous stem cell transplantation (ASCT), and the difficulty in collecting stem cells from patients who have had prolonged melphalan exposure led MP to be supplanted by single-agent therapy with pulsed dexamethasone and combination therapy with vincristine, adriamycin, and dexamethasone, in patients under 65 years of age.(3-6) More recently, thalidomide,(7-10) bortezomib,(11-13) and lenalidomide, a thalidomide analog, (14-17) have emerged as effective agents in the treatment of MM, dramatically altering the way the disease is treated. Two recently reported randomized trials, and multiple retrospective analyses have shown that compared to MP, induction therapy with dexamethasone alone or in combination with thalidomide produces higher response rates, and in older patients, improves survival. (18-19) Thus, for most newly diagnosed, transplant ineligible patients, treatment includes induction therapy with either MP or thalidomide and dexamethasone. Transplant eligible patients usually receive a thalidomide or bortezomib containing regimen. After transplant, patients who have not achieved a complete response are likely to receive some form of maintenance therapy.

Unfortunately, neuropathy occurs in up to 40% of patients with myeloma whose initial treatment includes thalidomide. In up to 7% of patients, these symptoms are >/= grade 3. The incidence is much higher in relapsing patients, and increases further in the presence of diabetes or amyloidosis. Similarly, bortezomib causes >/= grade 3 neuropathy in 8% of patients when given as salvage or front-line therapy. Preexisting neuropathy is a risk factor for higher rates and increased severity of treatment-related neuropathy in these patients. (20-25)

In the absence of curative therapy, nearly all patients with myeloma will eventually require single or combination therapy with these neuropathy causing agents. In some patients, the neuropathy can be of such severity that it affects treatment compliance and even results in the discontinuation of otherwise effective antineoplastic therapy. Treatment-induced neuropathy is thus an important barrier to overcome for successful chronic therapy of this disease.

The effects of cytokines on Schwann cells may explain the clinical presentation of chemo-neuropathy and account for the known risk and protective factors. Both myelinating and non-myelinating Schwann cells express receptors for TNF, IFN, IL-1 and IL-6 and activation of these receptors leads to activation of NFkB and c-jun pathways that in turn result in down-regulation of myelin synthesis, increased expression of the p75 NGF receptor, dedifferentiation, and proliferation (26-29). Exposure of peripheral nerves to inflammatory cytokines thus results in extirpation of myelin and perineural swelling like that observed in the early stages of Wallerian degeneration as well as that observed in neural biopsies from chemotherapy-treated animals and humans described above. These phenotypic changes have pronounced impact on A-Beta fiber function that is heavily dependent on extensive myelination, but less so on C-fibers, thus generating a clinical picture like that observed in the patient studies. Moreover, in that very rich sources of the pro-inflammatory cytokines are found in cells resident in the skin, such as tissue macrophages, Langerhans cells and most especially keratinocytes, that are in close proximity to myelinated nerve endings outside the blood brain barrier the die-back pattern is only to be expected. As individual Schwann cells become activated and exposed to pro-inflammatory cytokines, they themselves begin to synthesize and release pro-inflammatory cytokines (29-31), affecting neighboring Schwann cells and thus closing a positive feedback loop that can sustain the neuropathy. Prolonged or high dose exposure of Schwann cells leads to apoptosis which may further explain the persistence of pain in some chemotherapy patients (26). Finally, NGF, IGF, and NT-3, all of which offer protection to chemotherapy-induced pain in animals (32-34), inhibit NF-kB signaling (35) and prevent or reverse the effects of inflammatory cytokines on Schwann cells (36,37).

In vitro, cytokines are released from both animal and human tissues following exposure to chemotherapy drugs; and, co-administration of neurotoxic chemotherapeutic drugs with cytokines, for example vincristine in combination with GM-CSF, markedly increases the severity and magnitude of treatment-induced pain and other neurological impairments (38,39). Other studies show that cytokines IFN alpha/gamma, TNF-alpha, IL-1, and IL-6 are increased *in vitro* by cisplatin (40-42) and paclitaxel (43,44) as well as by ionizing and ultraviolet irradiation (45-47). The pattern of cytokine gene induction, synthesis and release induced by paclitaxel is identical to that induced by LPS (45,46). Cell sources for the cytokines induced by cisplatin and paclitaxel include macrophages, monocytes, tumor and endothelial cells (40,48-50). Neurons and glial cells are another potential source of pro-inflammatory cytokines (51-54) that have not yet been tested. Vincristine increases GM-CSF (55) and IL-15 and down-regulates TNF-alpha receptors (55). All three chemotherapy drugs directly activate the NF-kB signaling pathway that is shared with LPS, IL-1, IL-6, IFN and TNF(56).

While the specific causes of thalidomide and bortezomib induced peripheral neuropathy remain to be fully elucidated, inhibition of these pro-inflammatory cytokines may prevent or reduce the degree of neuropathy induced by these agents. To this end, the primary objective of this randomized Phase II clinical trial is to explore broad pro-inflammatory cytokine blockade, as rationale strategies for the prevention of treatment-induced neuropathy induced by thalidomide and/or bortezomib in previously untreated patients with myeloma.

One strategy to effect broad cytokine blockade is with minocycline, a semi-synthetic second-generation tetracycline derivative, that appears to exert a neuroprotective effect in animal models of central nervous system trauma and neurodegenerative disease. Preclinical data suggests that minocycline

modulates microglia, and limits immune cell activation and migration to sites of inflammation, thereby reducing subsequent release of cytokines, chemokines, lipid mediators of inflammation, matrix metalloproteinases (MMPs) and nitric oxide release. This reduces neural inflammation, thereby preventing apoptosis of neural cells. In addition, minocycline reduces activation of caspases including caspase-1 and caspase-3 which may further limit neural cell death.(57) Common side effects of the drug are light-headedness and vertigo. A rare but serious reported side effect is pseudo-tumor cerebri. Other adverse effects reported include serum sickness like reactions, ototoxicity, azotemia, pulmonary infiltrate formation with associated eosinophilia, and discoloration of the sclera or teeth.

In this study patients will be randomized to receive minocycline or placebo. The goal of this trial is to prevent treatment induced neuropathy in patients receiving induction therapy with thalidomide or bortezomib for multiple myeloma.

3.0 Patient Eligibility

Inclusion Criteria:

1) Newly diagnosed English speaking patients with symptomatic multiple myeloma who have received 1 or fewer treatment cycles of thalidomide or bortezomib, and who will receive thalidomide and/or twice-weekly schedule bortezomib as part of induction therapy for their multiple myeloma.

2) Age greater than or equal to 18 years

3) Able to render informed consent and to follow protocol requirements

4) Women must be postmenopausal (no menstrual period for a minimum of 1 year) or if they are of childbearing potential they must agree to use adequate birth control measures (e.g. abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, implantable or injectable contraceptives or surgical sterilization) during the study.

5) Men must agree to use adequate birth control measures (e.g. abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, implantable or injectable contraceptives or surgical sterilization) during the study.

Exclusion Criteria:

1) Hypersensitivity to tetracyclines

2) Poorly controlled or advanced diabetes mellitus (hemoglobin A1c >/= 8%)

3) Women who are pregnant or nursing.

4) Patients with peripheral neuropathy of >/= grade 2 by CTCAE v4.0.

5) Have a history of alcohol or substance abuse within the preceding 6 months that, in the opinion of the investigator, may increase the risks associated with study participation or study agent administration, or may interfere with interpretation of results.

6) Currently have any known malignancy other than multiple myeloma, or have a history of malignancy within the previous 5 years, with the exception of basal cell or squamous cell carcinoma of the skin that has been fully excised with no evidence of recurrence.

7) Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease.

8) Inability to use interactive voice recognition software due to physical limitations (e.g. hearing impairment).

4.0 Treatment Plan

4.1 Patient Registration
All patients will be registered in the Clinical Oncology Research System (CORe). The study will accrue a total of 142 patients (allowing a dropout rate of 10%) with 71 patients randomized to each of the two arms - placebo and minocycline. Prior to accruing the first patient, a randomization list matched to accrual numbers will be generated by a biostatistician in the Department of Symptom Research for all 142 patients, indicating to which group each patient is randomized. This list, containing the accrual number and treatment group information, will be given to Investigational Pharmacy. A password-protected backup list will be kept on the Department of Symptom Research computer server. This list will only be opened in case unblinding is needed.

The Investigational Pharmacy will keep the only list of patients' accrual numbers, patients' IDs, and randomization group assignments. When a patient is registered on study, the clinical research coordinator will notify the Investigational Pharmacy of the patient's accrual number and ID number. The Investigational Pharmacy will determine the randomization assignment information from the generated randomization list. The Investigational Pharmacy will see that the correct medication is dispensed to the patient. Patients will be randomized into one of the 2 possible arms. (See Section 4.2 Treatment Schedule)

In the event of a Grade 3-4 serious adverse event that may be related to the study medication, the treating clinician will contact the Investigational Pharmacy to determine the patient's randomization group.

4.2 Treatment Schedule
This is a double-blind, placebo-controlled Phase II study of minocycline vs. placebo in patients receiving an induction regimen of thalidomide and/or bortezomib for previously untreated multiple myeloma.

Patients will be randomized between 2 treatment arms:

Arm A: will receive a placebo of one dose on the first day of induction therapy for multiple myeloma, then doses every 12 hours for 10 weeks.

Arm B: will receive minocycline 200 mg orally for 1 dose, then 100 mg orally every 12 hours for 10 weeks beginning at initiation of induction therapy for multiple myeloma.

All patients in both study arms will receive standard instructions from their treating physicians and/or designees about the risk of development of peripheral neuropathy with thalidomide and bortezemab therapy, about the signs and symptoms of peripheral neuropathy, and about reporting signs and symptoms of peripheral neuropathy to their treating physicians. Symptomatic management of National Cancer Institute Common Toxicity Criteria Adverse Events version 4.0 (Appendix B), $\geq$ Grade 2 painful neuropathy (e.g. DULOXETINE HYDROCHLORIDE, GABAPENTIN, PREGABALIN) will be allowed on both arms of the study. As there are no standardized treatment guidelines for chemotherapy-induced peripheral neuropathy, the choice of treatment will be made at the discretion of the treating physician. However, a list of medications given for treatment of peripheral neuropathy, and the date each medication was started and stopped, will be collected by the clinical study coordinator at each clinic visit.

5.0 Dose Justification

5.1 Minocycline
Minocycline is currently approved by the US FDA for the treatment of bacterial infections. The dose and schedule of minocycline chosen for this study follows that used for this approved indication.

6.0 Background Drug Information

6.1 Minocycline

DESCRIPTION
Minocycline is a semi-synthetic tetracycline derivative for oral or intravenous use.

ADMINISTRATION
When taken orally, it should be administered with adequate fluids. Rapid IV infusion should be avoided

HOW SUPPLIED
Intravenous Powder for Solution: 100 MG
Oral Capsule: 50 MG, 75 MG, 100 MG
Oral Suspension: 50 MG/5 ML
Oral Tablet: 50 MG, 75 MG, 100 MG
a) Intravenous route
1) Reconstituted solutions of minocycline are stable at room temperature for 24 hours, but the solution should be administered immediately (King, 1993); (Prod Info Minocin(R), 2000c).
2) Stability data has been presented on a 0.1 milligram/milliliter solution of minocycline prepared in 5% dextrose or 0.9% sodium chloride at various temperatures for up to 1 week. The concentration of minocycline declined by 8% when stored at 24 degrees celsius for 1 week. There was only a 2% decline in concentration when minocycline was stored at 4 degrees celsius for 1 week (Pearson & Trissel, 1993a).
B) Oral route
1) Minocycline suspension can be stored at room temperature. It should be protected from freezing (Prod Info Minocin(R), 2000b).
2) Minocycline capsules should be stored at 15 to 30 degrees Celsius (59 to 89 degrees Fahrenheit) in an area free of light, moisture, and excessive heat (Prod Info Dynacin(R), 1996); (Prod Info Minocin(R), 2000a).
3) Minocycline pellet-filled capsules should be stored at 20 to 25 degrees Celsius (68 to 77 degrees Fahrenheit) in an area free of light, moisture, and excessive heat (Prod Info Minocin(R) pellet- filled capsules, 2000a).

CLINICAL PHARMACOLOGY

METABOLISM
MINOCYCLINE is metabolized to a significant degree, however, the nature of the metabolic products or sites of metabolism have not been elucidated with certainty (allen, 1976b)

PHARMACOKINETICS
Minocycline has a long serum half-life and can be administered at 12 hour intervals.

TIME TO PEAK CONCENTRATION
1) ORAL: 1 to 4 hours (Prod Info Dynacin(R), 1996b); (Prod Info Minocin(R), 2000a)(Simon et al, 1976; MacDonald et al, 1973).
a) Following a single dose of two 100 milligram (mg) MINOCYCLINE pellet-filled capsules to 18 healthy fasting adults, the Cmax ranged from 2.1 to 5.1 mcg/mL in 1 to 4 hours (Prod Info Minocin(R), 2000a)(Simon et al, 1976). Following a single dose of two 100 mg MINOCYCLINE capsules to 10 normal adult volunteers, the Cmax ranged from 0.74 micrograms per milliliter (mcg/mL) to 4.45 mcg/mL in one hour (Prod Info Minocin(R), 2000b).

ADVERSE EFFECTS

COMMON
Cardiovascular: Light-headedness
Neurologic: Dizziness, Vertigo

SERIOUS
Neurologic: Bulging fontanelle, Pseudotumor cerebri (rare)

7.0 Pretreatment evaluation

7.1 Within 7 days prior to the start of treatment the following studies will be required:

1.**History and Physical Examination** (including documentation of current medications and ECOG performance status

2. **Laboratory Studies**: CBC, ALT, AST, Total Bilirubin, Electrolytes, BUN, Creatinine, Beta HCG (serum or urine) if patient is a female of child bearing potential.

3. Additional Laboratory Studies
a) Human Cytokine Measurements. Blood samples (one tube of coagulated blood, 10 mL red top) for the cytokine assays will be obtained by venipuncture just before sensory testing. All cytokine analyses will be performed under the direction of Dr. Reuben. Blood samples will be collected by the designated research nurse and provided to Dr. Reuben's laboratory. Serum/plasma levels of multiple cytokines will be measured using a Multiplex Bead Immunoassay in conjunction a Luminex 100 analyzer (Luminex Corp., Austin, TX). Human cytokine/chemokine panels containing antibodies specific for the cytokines and proteins of interest are covalently linked to individual beads of a different fluorescent marker. When the beads are reacted with sera or plasma containing cytokines, the cytokines bind to the bead coated with the complementary antibody, and its unique fluorescent signature of the cytokine-bead complex is detected by the Luminex 100 analyzer. The cytokines to be measured will include IL: -1b, -1RA, -2, -4, -5, -6, -8, -10, -12, -15, IFN-a, IFN-g, TNF-a, TNF-R1, TNF-R2, VEGF, NF-kappa B, and b-FGF. In cases that the level of an individual cytokine can not be detected in serum by the bead assay, a high-sensitivity ELISA will be used.

b) MicroRNA in Plasma and Peripheral blood mononuclear cells (PBMC). To determine micro RNA, total RNA will be extracted from PBMC and plasma and microRNA array will be performed to identify specific miR of interest in batch analyses. Pre-plated 96-well plate arrays will be ordered from Applied Biosystems custom plating service to measure MiR-15a, -16, -21, -19a/b, -146a/b, -155, -181a/b, -222, -382, and 2 house keeping miRs (RNU-44 and -48) expressed in triplicates by peripheral blood mononuclear cells and in plasma. A 10mL purple top (EDTA anticoagulant) tube is required for micro RNA in both plasma and PBMC.

4. **Sensorimotor Evaluation.** Each zone of sensory disturbance or pain is examined for any physical changes such as scaling, finger clubbing, erythemia, etc, which are documented by digital photography. The areas of sensory disturbance are then physically probed by light touch with a camel hair brush and by manual massage to screen for the presence of allodynia or hyperalgesia. The following indices are then measured at the three test locations (finger tips, thenar eminence, volar forearm):

a) Heat and cold detection and pain threshold*.* The threshold for warm detection and heat pain will be determined using a computer controlled 3 X 3 cm peltier device in both Marstock (61) and double random staircase modes (62, 63) . The methods of limits approach will be the primary means to determine heat and cold pain thresholds in order to reduce the overall testing time, whereas the more time consuming double random staircase will be used to confirm the initial threshold measurement. Each heat ramp trial will start at a baseline temperature randomized between 33-35ºC. The heat stimulus is then increased without patient cuing at a rate randomized between 0.5-2.5ºC/s. Subjects are instructed to report when they detect warm, pain, or other. The computer is flagged on each report and returns to the baseline temperature with the stroke of the pain or other flag (64). This procedure is repeated three times with a randomized inter-stimulus interval between 90 and 180s. The threshold for each quality is defined as the mean of the three trials. No correction will be made for reaction time artifact. If a subject fails to reach a threshold before the cutoff temperature of 51.5ºC is reached, then this will be recorded as the heat pain threshold. The threshold for cool and cold-pain detection is determined in a similar manner, except that the temperature is decreased at a rate of 0.5-2.5ºC/s to a cutoff temperature of 4ºC held for 30 sec.
The double random staircase is used to confirm the thresholds obtained in the first method. The method of limits threshold is entered to the computer. Each staircase starts from a baseline temperature of 34ºC and the first step in each staircase is to a temperature 4ºC below the pre-programmed heat (or cold) pain threshold and held for 5 sec. Each stimulus is randomized between the two staircases. Changes within each staircase are based on the patient response to each step. A response of pain results in the next step being lowered in temperature by 0.5ºC, whereas a first response of no-pain or other results in repetition of the same step. A second response of no-pain or other within the same staircase results in an increase of 0.5ºC. The procedure ends when the same temperature is identified as painful within both staircases.

b) Touch detection thresholds*.* Touch detection thresholds are determined using the up/down method with calibrated von Frey monofilaments (65). Starting with a 0.5 mN force, the von Frey monofilament is applied for approximately 1 sec. If the subject fails to detect the stimulus, then the next higher force von Frey monofilament is applied. When the subject detects the presence of the stimulus, the next lower von Frey is administered. The up/down test sequence continues until the same force filament is detected for three additional applications. The force of that filament is then assigned as the touch threshold (64).

c) Sharpness threshold and pain to needle probes*.* Sharpness detection is determined using a method of limits and a method of constant stimuli. In each, a 30 gauge needle (200 µm diameter) filed to produce a flat, cylindrical end is applied to the skin using either a continuous ramped force or weighted intervals, respectively. In the first method, the needle probe is mounted onto a mechanical microdrive that is centered below a 3cm diameter hole in the surface of a portable table. The table surface is padded to allow the patient to place the targeted body part over the hole while the remainder of the limb is comfortably supported. The microdrive is advanced until contact with the surface of the skin is detected by a pressure transducer that is mounted between the needle and the microdrive head stage. A stimulus run is initiated by advancing the microdrive at a rate of 75 µm/s when applied to the finger tips and at a rate of 150 µm/s when applied to the thenar eminence or the volar forearm. These rates of advance are based on preliminary studies demonstrating that these generate a force ramp of approximately 15 mN/s at each site. Threshold in normal volunteers is reached at all three sites at 150.71 ± 20.3 mN force corresponding to a displacement of 750 µm on the finger tips, 1.65 mm on the thenar eminence and 1.8 mm on volar skin. A cut-off will be set at 500 mN so that the probe will not damage the skin. This value will be recorded for any patients failing to detect the stimulus up to this force.
In the second method, brass weights are fitted into the Luer connection of a needle and this assembly is placed inside a 10 cc syringe so that the needle projects out of the tip of the syringe while still moving freely within the syringe (66). The needle is applied to the skin surface and forces of 80, 160, 320, 640, 1280, 2560 mN are generated by gravity on separate weighted needles. Each stimulus is applied in ascending order for 1 sec. The subjects are instructed to indicate if the stimulus produces a sensation of touch, pressure, sharpness, pain, or other. The threshold for sharpness is recorded at the first report of sharp or pain.

d) Blunt pressure*.* A 3mm rounded nylon probe mounted onto a force gauge with an automatic stop marker (Correx Pressure Gauge #31-009-4) is applied with steady slow pressure onto each test site to a maximum of 200g. The patient is cued to report the onset of pressure, pain, or other, and the gauge measurement of this report is recorded.

e) Slotted peg board test. A slotted peg board test will be used to assess sensorimotor function of myelinated fibers (68,69). Patients will fill a five-by-five slotted pegboard in an ordered fashion, either across rows or down columns. The times for both dominant and non-dominant hands are recorded(64).

f) Treatment-Related Neuropathy Assessment Scale. This 11-item patient reported outcome measure provides an additional opportunity to capture chemotherapy induced neurosensory changes including hot or burning sensations in the hands and feet, sensations of pins and needles in the arms and legs, sensations of electric shock, pain when touching cold things and trouble with balance due to loss of feeling in the legs or feet. (Appendix K)

5. Neurocognitive Testing

a) *Attention span*. Digit Span (70) will be used to measure concentration, attention, and immediate memory. The test requires the repetition of number strings forward and backwards. Lower scores are obtained by persons with an attention deficit or anxiety.

b) *Graphomotor speed*. The Digit Symbol (70) test will be used to measure visual-motor speed and short-term visual memory. This test requires symbols to be matched with numbers or shapes according to a key.

c) *Memory*. The Hopkins Verbal Learning Test (71) yields measures of: a) verbal learning (sum of trials 1-3), b) retention, and c) recognition ability. During this test a list of 12 words from three taxonomic categories is presented to the subject with words read aloud at the rate of approximately one word every two seconds. The test includes three list learning trials. Delayed recall is assessed 20-25 minutes later. Immediately after administration of the Delayed Recall trial, a forced-choice recognition test is administered. The recognition test includes the 12 target words plus 12 distractors (six semantically-related and six semantically -unrelated).

d) *Verbal fluency*. The Controlled Oral Word Association Test (72)is a measure that allows the subject 60 seconds to generate a list of words, excluding proper nouns, beginning with a particular letter of the alphabet.

e) *Visual-motor speed*. The Trail Making Test Part A (73) is a speed test of visuomotor sequencing, the patient draws lines to connect numbered circles in order.

f) *Executive Function*. Trail Making Test Part B (73) requires alternating letter-number connecting. It is a measure of attentional switching. However, its functional and anatomical specificity is affected by several factors, including speed, visual search, and the patient's ability to simultaneously maintain two sequences in their mind.

g) *Motor dexterity*. The Grooved Pegboard (73) test assesses special concepts, hand-eye coordination and concentration. Subjects are required to orient 25 pegs to slots in a grooved pegboard. Subjects are scored on the time taken to insert all pegs correctly using dominant and non-dominant hands.

h) *Mood*. The Beck Depression Inventory-II (74) is a 21-question multiple choice survey that asks questions about depression symptoms including emotions such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. Participants are asked to rate how they have been feeling for the past two weeks. Each answer is given a value

of 0 to 3. The scoring is as follows: 0-13 - minimal depression; 14-19 - mild depression; 20-28 -moderate depression; and 29-63 - severe depression. Higher total scores indicate more severe depressive symptoms (see Appendix M).

Beck Anxiety Inventory (75) is a 21 item survey, in which each item describes a common symptom of anxiety. The respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3. The items are summed to obtain a total score that can range from 0 to 63. This survey is used to discriminate anxiety from depression (see Appendix N).

6. **Epworth Sleepiness Scale to screen for daytime sleepiness** (See appendix E).

7. **M. D. Anderson Symptom Inventory (MDASI-MM module) scores.** The core MDASI-MM module is a brief, easily understood instrument that provides a measure of the intensities of 13 cancer-related symptoms. Patients will be asked to rate the intensity of physical, affective, and cognitive symptoms on 0 to 10 numeric scales from “not present" (score of 0) to "as bad as you can imagine" (score of 10). Patients will also rate the amount of interference with daily activities caused by symptoms on 0 to 10 numeric scales from "did not interfere" (score of 0) to interfered completely (score of 10) (See Appendix F). Six symptom items determined by physicians and nurses in the Lymphoma/Myeloma and Blood and Marrow Transplantation Departments to be important for the assessment of patients with multiple myeloma and patients who are post-transplant will be added to the core MDASI-MM module for this study. The symptoms to be assessed by the core MDASI-MM module include: pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, numbness, constipation, muscle weakness, diarrhea, mouth or throat sores, rash, and trouble concentrating. The six additional items assessing symptom-related interference in general activity, mood, work, relation with others, enjoyment of life and walking. The MDASI-MM module will be administered in person or by an interactive voice response (IVR) telephone system. The IVR system will asks patients to rate each symptom and interference item on the 0-10 numeric scales using the keypad of a touch-tone telephone. (60)

8. **Assessment of toxicity** as defined by the National Cancer Institute Common Toxicity Criteria, version 4.0

8.0 Evaluation During Study

8.1 While on study, patients will complete weekly MDASI (weeks 1-9).

8.2 From the time of clinical evaluation of response to each cycle of multiple myeloma therapy but prior to the administration of the next cycle (excluding the start of cycle 1 since covered by pre-treatment evaluation testing) the following assessments will be performed, except as noted below for Sensorimotor Evaluation:

1. History and Physical (including documentation of current medications and ECOG performance status).

2. Laboratory studies: CBC, ALT, AST, Total Bilirubin, Electrolytes, BUN, Creatinine.

3. Additional laboratory assays: a) Serum cytokine levels: IL: -1b, -1RA, -2, -4, -5, -6, -8, -10, -12, -15, IFN-a, IFN-g, TNF-a, TNF-R1, TNF-R2, VEGF, NF-kappa B, and b-FGF, (b) microRNA MiR-15a, -16, -21, -19a/b, -146a/b, -155, -181a/b, -222, -382, and 2 house keeping miRs (RNU-44 and -48) expressed by peripheral blood mononuclear cells and in plasma.

4. Sensorimotor Evaluation (this is to be performed at a timepoint that falls between the clinical evaluation of response to each cycle of multiple myeloma therapy and within 7 days of starting the next cycle).

5. Epworth Sleepiness Scale

6. Assessment of Toxicity (See appendix B)

9.0 End of Study Evaluation

At the end of the study period +/- 10 business days, the following testing will be performed:

1. History and Physical (including documentation of current medications and ECOG performance status).

2. Laboratory studies: CBC, ALT, AST, Total Bilirubin, Electrolytes, BUN, Creatinine.

3. Additional laboratory assays: a) Serum cytokine levels: IL: -1b, -1RA, -2, -4, -5, -6, -8, -10, -12, -15, IFN-a, IFN-g, TNF-a, TNF-R1, TNF-R2, VEGF, NF-kappa B, and b-FGF, (b) microRNA MiR-15a, -16, -21, -19a/b, -146a/b, -155, -181a/b, -222, -382, and 2 house keeping miRs (RNU-44 and -48) expressed by peripheral blood mononuclear cells and in plasma.

3. Sensorimotor Evaluation

4. Neuro-cognitive testing

5. Epworth Sleepiness Scale

6. Assessment of Toxicity (Appendix B)

7. Documentation of response to induction therapy for multiple myeloma (by testing performed by the treating physician as part of routine evaluation of multiple myeloma) will be collected at the end of the study period +/- 10 business days. Response will be documented according to the International Uniform Response Criteria for Multiple Myeloma. (Appendix J)

10.0 Criteria for Removal from the Study

1. Development of a serious adverse event related to the study drug
2. Inability to comply with protocol requirements
3. Discontinuation of treatment with thalidomide or bortezomib

4. Completion of study

11.0 Statistical Considerations

The primary outcome of this study is the difference between touch detection thresholds from the sensorimotor evaluation at baseline and after 10 weeks of induction therapy. Secondary outcomes are the change in the mean value of patient-reported MDASI-MM pain and numbness scores from baseline to week 10 posttreatment. Cytokines, symptoms, and neurosensory testing will be done prior to each cycle of multiple myeloma therapy +/- 3 business days until week 10. There will be 71 patients(allowing a 10% dropout rate) in each group (minocycline and control). The total sample size will be 142 patients (allowing for a 10% dropout rate).

Touch detection measurements, cytokine levels, and symptom measurements will be summarized by descriptive statistics (mean, median, quartiles) at each time point for both treatment groups. For each measurement, the mean values over time will be graphically presented for both groups in the same plot.

To evaluate the efficacy of the treatment groups, changes in touch detection measurements from baseline to week 10 will be calculated, and a linear model will be used to test the association between the treatment group and the change in touch detection values from baseline. The following covariates will be included in the model: symptom intervention treatment, primary therapeutic treatment (thalidomide vs. bortezomib), mode of administration for bortezomib (subcutaneous or i.v.) baseline MDASI-MM score, age, race, body mass index, and other available demographic variables, performance status, and

the Charlson comorbidity index. In addition, we will perform separate analyses in the subcutaneous and i.v. subsets of patients.

Change in neuropathy scores from baseline to week 10 will also be calculated and a linear model similar to that described in the preceding paragraph will be used to test the effect of treatments on the MDASI-MM scores. The same set of covariates will be used in this model.

Scatterplots will be created to visually examine the relationship between each touch detection or MDASI-MM measurement and the NF-kappaB, IL-6, TNF-alpha and other serum proinflammatory cytokines. If the data are normally distributed, Pearson's correlation coefficient will be used to assess the association between the quantitative sensory testing/MDASI-MM measures and cytokine levels. Spearman's correlation coefficient will be used if the data are not approximately normally distributed. These analyses will be repeated for each of the cytokines at each collection time point.

To compare the NF-kappaB, IL-6, IL-1, TNF-alpha, and other serum proinflammatory cytokine levels across the treatment groups, an analysis of variance (ANOVA) model will be used to determine if there are any differences between the treatment groups.

If the distribution of the outcome variables cannot reasonably be regarded as Gaussian, we will investigate transformations of both response and explanatory variables to a scale upon which a Gaussian model can be employed. If such a scale cannot be identified, we will instead use ordinal regression models after identifying appropriate categories for response variables, or will include explanatory variables into the regression models as factor variables. If the paired differences in measurements of any primary outcome variable cannot reasonably be assumed to be normally distributed, tests for treatment differences will be conducted using the 2-sample Wilcoxon test (Gibbons & Chakraborti, 2003).

Sample size justification. Because repeated-measures data for threshold values collected from induction patients are not available, we will assume for design purposes that the between-individual variation for healthy volunteers is at least 50% as large as the longitudinal variation between measurements on the same study patients. Under the null hypothesis of no treatment effect, we assume that the measured difference in touch threshold for a randomly selected subject is normally distributed with mean M and standard deviation 0.131648 g. Under the alternative hypothesis, we assume that the increase in touch threshold will be 0.065824 g less for patients in each of the treatment arms than for patients receiving best supportive care. Assuming that 64 patients are enrolled in each arm, we will have 80% power to detect a difference of 0.065824 g, a medium effect size equivalent to half a standard deviation in a 5% significance test. We regard this sample size/power estimate to be conservative owing to the fact that the standard deviation between measurements collected from the same patients (from the mean change in response) is likely to be smaller than 0.131648 g.

Current funding for this study is due to end on 8/31/2013. In order to determine whether the study should be discontinued and the results reported or if additional methods of funding to continue the study should be sought, we request interim analyses for futility/superiority. Three interim analyses will be performed after 25%, 50%, and 75% of the patients are evaluable. The trial will be stopped for futility if the absolute nominal critical point for the change in fingertip QST threshold analysis is less than 0.011 (32 patients), 0.41 (64 patients), or 1.28 (96 patients). Conversely, the trial will be stopped for superiority if the absolute nominal critical point for the change in fingertip QST threshold analysis is greater than 4.33 (32 patients), 2.96 (64 patients), or 2.36 (96 patients). At the end of the trial, superiority will be claimed if the absolute nominal critical point for the change in fingertip QST threshold analysis is greater than 2.01. The stopping boundaries were computed using the O'Brien-Fleming approach. If the numbers of patients at the interim analysis timepoints are different from above, the stopping boundaries will be adjusted using the Lan-DeMets spending function. With 64 patients in each treatment arm, the power decreased slightly (from 80% to 77%) as a result of the added interim analyses, however, the sample size will not be adjusted to account for this addition.

Randomization. When this study first opened, randomization was performed by a list provided to the study pharmacy. All patients received intravenous administration of bortezomib. The protocol is currently being changed (June 2012) to allow for subcutaneous administration in addition to intravenous administration of bortezomib. After this change is approved, randomization to minocycline or placebo for this trial will be implemented on the M.D. Anderson Department of Biostatistics Clinical Trial Conduct website found at: https://biostatistics.mdanderson.org/ClinicalTrialConduct/. There will be two separate arms, one for patients receiving subcutaneous administration and the other for patients receiving intravenous administration. For intravenous administration, randomization will be performed using randomized blocks of size 2. For subcutaneous administration, randomization will be performed using randomized blocks of size 6. The Department of Biostatistics will set up the randomization on the website.

Safety Monitoring in Experimental Arm

The following decision criteria will be applied only to the experimental arm after each cohort of 10 experimental treatment patients has been evaluated at week 10, up to the 64th experimental treatment patient. Under the rate restrictions noted above, stopping boundaries for neuropathy, infection or objective response (OR) are specified below.

First, OR is defined as a score at the end of study assessment of "stringent complete response", "complete response", "near complete response", "very good partial response", or "partial response". Patients who drop out of the study before the completion of two cycles of therapy and who do not experience a partial or complete response will be considered failures with respect to this endpoint. Partial response (PR) or better, as defined by the international uniform response criteria for multiple myeloma as follows:

>/=50% reduction of serum M-protein and reduction in 24-h urinary M-protein by>/=90% or
to <200mg per 24 h.
If the serum and urine M-protein are unmeasurable, a >/=50% decrease in the difference
between involved and uninvolved FLC levels is required in place of the M-protein criteria
If serum and urine M-protein are unmeasurable, and serum free light assay is also
unmeasurable, >/=50% reduction in plasma cells is required in place of M-protein,
provided baseline bone marrow plasma cell percentage was >/=30%
In addition to the above listed criteria, if present at baseline, a >/=50% reduction in the size of soft tissue plasmacytomas is also required. (78)

We propose that the trial be stopped if there is evidence that the OR rate with the experimental treatment is less than the OR rate associated with the standard of care, 65%, with probability exceeding .95. We propose to monitor this probability in the minocycline arm after the treatment of every tenth patient. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients with OR in experimental arm) / (# patients evaluated in experimental arm)
≤ 3/10, 9/20, 14/30, 20/40, 26/50, or 32/60.

The probabilities correspond to the posterior probabilities that would be obtained by placing a beta prior with parameters (0.65,0.35) on the OR rate.

Next, we propose that the trial be stopped if the probability that the neuropathy rate in the experimental arm exceeds 40% exceeds .95. Neuropathy is defined as a positive change in the numbness score between the baseline assessment and the end of study assessment. Patients with no baseline or follow-up assessments will not be included in this analysis. We also propose to monitor this probability after the treatment of every tenth patient in the experimental arm. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients with neuropathy in experimental arm) / (# patients evaluated in experimental arm)
≥ 7/10, 12/20, 17/30, 22/40, 26/50, or 31/60.

The probabilities correspond to the posterior probabilities that would be obtained by placing a beta prior with parameters (0.40,0.60) on the neuropathy rate.

Finally, we propose that the trial be stopped if the probability that the infection rate in the experimental arm exceeds 10% exceeds .95. Infection is defined as the experience of a Grade 1 or higher infection at any time from week 2 through the end of the study. All patients with at least one post-baseline assessment of toxicity will be included in this analysis. We also propose to monitor this probability after the treatment of every tenth patient. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients experiencing infection in experimental arm) /
(# patients evaluated in experimental arm)
≥ 4/10, 5/20, 7/30, 8/40, 10/50, or 11/60.

The probabilities correspond to the posterior probabilities that would be obtained by placing a beta prior with parameters (0.10,0.90) on the infection rate.

Design Operating Characteristics

Table 1. Operating Characteristics for Monitoring Rules

Actual ORR, Neuropathy, Infection Rate	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th percentiles		
.65, .40, .10 (acceptable target rates)	0.30	50	64	64
.65, .20, .10 (good neuro. rate)	0.20	64	64	64
.65, .60, .10 (poor neuro. rate)	0.96	10	20	30
.50, .60, .10 (poor ORR & poor neuro. rate)	0.99	10	20	20
.50, .40, .10 (poor ORR)	0.85	20	20	50
.65, .40, .20 (poor infection rate)	0.81	20	30	60
.30, .40, .20 (poor ORR & high infection rate)	1.00	10	10	20
.65, .20, .05 (good neuro & infection rates)	0.11	64	64	64
.65, .50, .20 (poor neuro & infection rates)	0.91	10	20	40

Sample Size Justification

Given an estimated 10% drop-out rate, the adjusted sample size is now 128/0.9=142.

12.0 References

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